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Title

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Permalink

<https://escholarship.org/uc/item/404458mj>

Journal

Stroke, 47(12)

ISSN

0039-2499

Authors

Lyden, Patrick
Weymer, Sara
Coffey, Chris
[et al.](#)

Publication Date

2016-12-01

DOI

10.1161/strokeaha.116.013881

Peer reviewed



Published in final edited form as:

Stroke. 2016 December ; 47(12): 2979–2985. doi:10.1161/STROKEAHA.116.013881.

Selecting Patients for Intra-arterial Therapy in the Context of a Clinical Trial for Neuroprotection

Patrick Lyden, MD¹, Sara Weymer², Chris Coffey, PhD³, Merit Cudkowicz, MD, MSc⁴, Samantha Berg, BA⁴, Sarah O'Brien, MPH³, Marc Fisher, MD⁵, E. Clarke Haley, MD⁶, Pooja Khatri, MD, MSc⁷, Jeff Saver, MD⁸, Steven Levine, MD⁹, Howard Levy, MD, PhD¹⁰, Marilyn Rymer, MD¹¹, Lawrence Wechsler, MD¹², Ashutosh Jadhav, MD, PhD¹², Elizabeth McNeil, MD, MSc¹³, Salina Waddy, MD¹³, and Kent Pryor, PhD²

¹Cedars-Sinai Medical Center, Los Angeles

²ZZ Biotech, LLC, Houston

³The University of Iowa, Iowa City

⁴Massachusetts General Hospital, Neurological Clinical Research Institute, Boston

⁵Beth Israel Deaconess Medical Center, Boston

⁶University of Virginia, Charlottesville

⁷University of Cincinnati, Cincinnati

⁸David Geffen School of Medicine, University of California, Los Angeles

⁹State University of New York –Downstate Medical Center, Brooklyn

¹⁰Consultant, ZZ Biotech, LLC

¹¹The University of Kansas Hospital, Kansas City

¹²University of Pittsburgh Medical School, Pittsburgh

¹³National Institutes of Health, National Institute of Neurological Disorders and Stroke

Abstract

Background and Purpose—The advent of intra-arterial neurothrombectomy (IAT) for acute ischemic stroke opens a potentially transformative opportunity to improve neuroprotection studies. Combining a putative neuroprotectant with recanalization could produce more powerful trials but could introduce heterogeneity and adverse event possibilities. We sought to demonstrate feasibility of IAT in neuroprotectant trials by defining IAT selection criteria for an ongoing neuroprotectant clinical trial.

Methods—The study drug, 3K3A-APC, is a pleiotropic cytoprotectant and may reduce thrombolysis associated hemorrhage. The NeuroNEXT trial NN104 (RHAPSODY) is designed to

Corresponding author: Patrick Lyden, Department of Neurology, 127 S San Vicente Blvd, AHSP A6417, Los Angeles, CA 90048, 310 926 1591, lydenp@cshs.org.

Disclosures

The remainder of the authors have no disclosures.

establish a maximally tolerated dose of 3K3A-APC. Each trial site provided their IAT selection criteria. An expert panel reviewed site criteria and published evidence. Finally, the trial leadership designed IAT selection criteria.

Results—Derived selection criteria reflected consistency among the sites and comparability to published IAT trials. A protocol amendment allowing IAT (and relaxed age, NIHSS, and time limits) in the RHAPSODY trial was implemented on June 15, 2015. Recruitment before and after the amendment improved from 8 enrolled patients (601 screened, 1.3%) to 51 patients (821 screened, 6.2%), OR [95%CL] of 4.9 [2.3,10.4], $p<0.001$). Gross recruitment was 0.11 patients/site/month vs. 0.43 patients/site/month, respectively, before and after the amendment.

Conclusions—It is feasible to include IAT in a neuroprotectant trial for acute ischemic stroke. Criteria are presented for including such patients in a manner that is consistent with published evidence for IAT while still preserving the ability to test the role of the putative neuroprotectant.

Clinical Trial Registration—Clinical Trial Registration-URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT02222714.

Clinical trials of neuroprotection for acute ischemic stroke, including rapid pre-hospital treatment, continue to fail. Possible contributors to this failure include the unsuitability of pre-clinical animal models¹, inadequate clinical trial design^{2, 3}, and inappropriate patient selection⁴. One of the most obvious and potentially powerful differences between animal and human neuroprotection studies is the influential role of recanalization/reperfusion. Recanalization refers to the re-opening of the principal artery supplying a vascular territory; reperfusion implies successful restoration of flow in the microvasculature. Recanalization without reperfusion fails to salvage brain after larger artery occlusion⁵. Pre-clinical studies repeatedly document that putative neuroprotectants provide greater benefit when combined with recanalization⁶. Many neuroprotectants show benefit in animal stroke models, but they all work best if given in combination with recanalization⁷. In contrast, documentation of arterial recanalization has not been required during human neuroprotection trials, and this could be one of the many reasons for clinical trial failures. Even after the advent of intravenous thrombolysis as an effective stroke therapy⁸, the typical clinical neuroprotectant stroke trial did not require documentation of successful recanalization as an enrollment criterion. If recanalization enhances the chance of successful neuroprotection, then the failure of so many stroke neuroprotection trials appears less surprising.

The advent of intra-arterial neurothrombectomy (IAT) for acute ischemic stroke opens a potentially transformative opportunity for improved study of neuroprotection. Combining a putative neuroprotectant with IAT could result in more powerful clinical trials, since all enrolled patients would have documented recanalization. On the other hand, allowing IAT in a clinical trial brings additional heterogeneity into the response outcome variable; introduces additional adverse event possibilities; and may limit generalizability of the trial results to centers that offer such therapy. As well, the published trials of IAT used a wide variety of inclusion/exclusion criteria, possibly making it difficult to design a clinical trial protocol that is consistent with published data^{9, 10}. Health organizations and professional societies have published guidelines for clinical implementation of IAT that seek to allow a wide range of options for physicians^{11, 12}. Wider latitude of treatment options allows individual physicians

to personalize their approach to each patient with acute ischemic stroke¹³, but practice variation among clinical trial study sites could introduce variation in the primary outcome sufficient to obscure treatment benefit or adverse effects of the study therapy¹⁴. The different, competing priorities of a clinical trial compared to clinical practice are summarized in Table One. Thus, the clinical trial design and protocol must specify a range of IAT treatment options that is sufficient to allow sites to use the therapy in a wide variety of patients without introducing excessive variability into the primary efficacy and safety outcomes.

We sought to define IAT selection criteria for an ongoing clinical trial of a putative neuroprotectant. The study drug takes advantage of the neuroprotective and vasculoprotective effects of activated protein C (APC), which is naturally active at the protease activated receptor-1 (PAR1)¹⁵. To avoid anticoagulation without changing the cytoprotective effects, the native APC structure was mutated in a targeted manner, such that 3 lysines were replaced by alanines removing >90% of the anticoagulant activity with preserved cytoprotection¹⁶. The resultant molecule, 3K3A-APC, exhibits considerable cytoprotective effects *in vitro* and in animal stroke models. 3K3A-APC protects neurons, astrocytes and endothelial cells directly, via action on the transmembrane G-coupled protein PAR1, but also shows vasculoprotective effects that could be interpreted as protection from ‘reperfusion injury’¹⁷. The drug shows greatest effect when combined with recanalization, and is effective after treatment delay of up to 12 hours after stroke onset¹⁸. 3K3A-APC has satisfied the Stroke Treatment Academic Industry Roundtable (STAIR) suggestions for pre-clinical drug assessment and has an established safety and pharmacokinetic profile in human volunteers^{19, 20}. The NeuroNEXT trial NN104 (RHAPSODY) is a dose-escalation trial designed to establish a maximally tolerated dose of 3K3A-APC (Protocol synopsis in Supplement). Although 3K3A-APC exhibits beneficial effect after permanent occlusion, the effect is greater in pre-clinical models that include recanalization^{18, 19, 21}. Thus, the RHAPSODY trial provides an opportunity to test whether allowing IAT (and thereby documenting recanalization) contributes favorably or negatively to clinical trial recruitment. We convened a panel of experts in both clinical trial design and IAT to review and critique proposed inclusion/exclusion criteria. Shortly after the publication of the key IAT studies, we surveyed our clinical trial sites to assess their local implementation of IAT selection criteria. Based on the summarized published primary results and published society guidelines, expert reviews, and local implementation at our sites, we defined IAT selection criteria for RHAPSODY. We adopted a clinical trial protocol amendment to allow IAT based on these selection criteria, and carefully monitored the implementation of the amended protocol in the study sites. Here we report on the results of the review process and the impact of the amendment on study recruitment.

METHODS

The RHAPSODY trial (A multi-center, Phase 2 study using a continual reassessment method to determine the safety and tolerability of 3K3A-APC, a Recombinant Variant of Human Activated Protein C (APC), in combination with tissue plasminogen activator (tPA), mechanical thrombectomy or both in moderate to severe acute ischemic stroke, NCT02222714) is a multicenter, prospective, randomized, controlled, double-blinded Phase

2 study intended to evaluate the safety, pharmacokinetics and preliminary efficacy of 3K3A-APC following tPA or mechanical thrombectomy or both in participants with moderate to severe acute ischemic stroke. Approximately 100 participants will be randomized, which includes 88 participants in groups of four randomized to either 3K3A-APC or placebo (3:1 ratio) and additional placebo participants enrolled during safety review pauses. This study utilizes a modified version of the continual reassessment method (CRM) to establish a maximum tolerated dose (MTD)²². For the purposes of this study, we assumed an established background symptomatic intracerebral hemorrhage (sICH) rate of 3–6%^{23–28}. Correspondingly, the MTD is defined as the highest dose with a dose limiting toxicity (DLT) rate of 10% or less. Participants are enrolled at the dose estimated from the assumed dose-response model and prior data to be closest to the MTD. Dose-limiting toxicities are assessed from the first dose to 48 hours following the last dose of study treatment. An elevation of PTT, sICH, systemic bleeding requiring transfusion, or hepatic toxicity that appears “related” to study treatment is considered a DLT. Abnormal laboratory values and any event that prompts cessation of study drug are evaluated as a possible DLT as well.

3K3A-APC is administered as a 100 mL IV infusion over 15 minutes every 12 hours (\pm 1 hour) for 5 doses. Four dose levels of 3K3A-APC will be considered: 120, 240, 360, and 540 μ g/kg. Matching placebo, visually indistinguishable from the drug, is administered in the same manner as the active product. The drug may not begin until 30 minutes after the end of the rt-PA infusion, for safety reasons, and no later than 120 minutes following completion of rt-PA infusion or initiation of mechanical thrombectomy (skin puncture), whichever is sooner, although investigators are encouraged to begin study drug infusion as soon as possible. Patients will be examined on Days 7, 14, 30 and 90 for safety and outcome. Participants are not considered part of the intent-to-treat (ITT) cohort until they receive any amount of 3K3A-APC or placebo. Thus, subjects who become ineligible (e.g. rapid responder whose NIHSS drops to <5) between randomization and initiation of study drug will be removed from the study and replaced. Detailed brain imaging is required prior to enrollment, at 24 hours, 7d, 30d, and 90d after enrollment, and will be analyzed for ischemic stroke size and hemorrhagic transformation.

Following the publication of studies reporting efficacy of IAT, we sought to assess the readiness of our study sites to include IAT in the treatment of enrolled patients. Each site provided any written guidance they used for specifying the patients they would consider eligible for IAT therapy. The results were summarized and sites that provided insufficient responses were contacted and asked to consider re-submitting. Next we assembled a panel of experts including principal investigators of some of the main IAT publications. The IAT selection document from each site was then reviewed and approved, rejected, or queried. Finally, using the input from the expert panel and the sites, the trial leadership designed study selection criteria for allowing IAT treated patients. Clinical trial recruitment was tracked before and after adoption of the protocol amendment. Additional changes implemented as part of the same protocol amendment were: extended the upper time window for administration of investigational drug from 90 to 120 minutes; extended the upper age range from 80 to 90; broadened the NIHSS range to ≥ 5 (from 7–20 previously). Criteria specific to IAT were also added: onset time to arterial puncture time < 6 hours and a

baseline CT revealing large core occlusions as defined by local protocol, ASPECTS or CT perfusion.

RESULTS

The key variables that influence efficacy and safety outcomes included in the published IAT trials are summarized in Table Two. Despite very different trial designs, the 5 trials actually enrolled samples that showed relatively consistent age, severity, and times to important milestones. The unexpected demographic consistency among these trials allows some specificity in designing clinical trial selection criteria.

The most critical factor influencing outcome after IAT is the incidence of successful recanalization. The main trials' recanalization rates are summarized in Table Three. Due to a wide variation in the method for determining recanalization, the rates summarized in Table Three are not uniformly comparable among the trials. All trials except ESCAPE used the mTICI score to assess recanalization in the intervention arm; ESCAPE used the TICI score. ESCAPE used the mAOL score to assess recanalization on repeat CTA (within 2–8 hrs of tPA) in the control arm; some other trials assessed recanalization/reperfusion in the control arm (not in all patients) after 24 hrs^{29, 30}. The critical safety outcomes include symptomatic intracerebral hemorrhage (sICH) and mortality. As shown in Table Three, the rate of sICH in the published IAT trials is comparable, or perhaps lower, than that seen in prior trials of IV thrombolysis. Mortality is similarly comparable to published trials of intravenous thrombolytic therapy.

After reviewing the assembled protocols from our study sites, as well as the results from published IAT trials, we derived a set of selection criteria that reflect consistency among the sites and comparability to the published IAT trials (Table Four). The protocol amendment allowing IAT (as well as relaxed age, NIHSS and time limits) in the RHAPSODY trial was adopted on May 1, 2015 and fully implemented at all sites by June 18, 2015. For the purposes of this analysis, we examined recruitment as of February 22, 2016. Recruitment before and after the amendment is shown in the Figure and in Table Five, which document considerable improvement in trial recruitment. Prior to the amendment, 8 patients were enrolled from 601 screened patients (1.3%) while after the amendment, 51 (2 IAT only, 25 IV rt-PA with IAT, and 24 IV rt-PA only) patients were enrolled from 821 screened patients (6.2%) with no change in the number of sites that were recruiting. Clinical trial recruitment depends on the number of active enrolling sites as well as the inclusion/exclusion criteria: the gross recruitment rate prior to the amendment was 0.11 patients/site/month, and after the amendment 0.43 patients/site/month. The final version of the RHAPSODY patient selection criteria is listed in the Supplement.

DISCUSSION

We sought to incorporate IAT into a clinical trial of neuroprotection for acute ischemic stroke. To our knowledge, there is no previous demonstration of the feasibility of this approach. Based on a summary of the published IAT trials and the selection criteria in use at 15 clinical trial study sites, we identified a range of acceptable selection criteria that could

be used in similar trials (Table Four). After implementing these criteria, as well as relaxed age, NIHSS and timing limits, trial recruitment accelerated dramatically (Figure). The data suggest that it is feasible and likely quite desirable to allow IAT in the context of a neuroprotectant stroke trial.

A plethora of putative neuroprotectants has emerged from pre-clinical testing, and many have shown early promise in small Phase 1 or Phase 2 trials. After testing in large, adequately powered, properly blinded and randomized pivotal trials, however, no neuroprotectant strategy has proven successful³¹. Pre-clinical studies typically include recanalization (although permanent vessel occlusion can be modeled) and combining a putative neuroprotectant with recanalization may provide the greatest chance for success. Some putative neuroprotectants successfully reduced infarct volumes in animals only if administered prior to recanalization/reperfusion. Such drugs might not be practical for clinical use in which recanalization with iv rt-PA or IAT must occur as quickly as possible after hospital arrival. Clinical trialists designing protocols for such agents may therefore wish to modify the selection criteria offered here.

Other differences between human and pre-clinical studies also matter: such experimental models typically involve young animals free of co-morbid conditions (e.g. diabetes, hypertension) that impact outcome after stroke, although the putative compound in the RHAPSODY trial, 3K3A-APC, has shown effectiveness in aged and in hypertensive animals¹⁸. Another critical factor in demonstrating neuroprotection is timing: drugs that show benefit in experimental models when given within minutes or an hour of recanalization have rarely been so tested in clinical trials. In RHAPSODY we require study drug infusion as soon as possible after consent, but no later than 120 minutes after skin puncture (or rt-PA completion). In this way, we suggest the protocol is optimized to show benefit since the drug will be combined with proven recanalization as verified during IAT. An alternative approach would be to require recanalization prior to study-drug treatment, thus limiting generalizability to patients who receive IAT alone or rt-PA plus IAT. This approach could be the ideal one, especially for a treatment in which pre-clinical testing suggests recanalization is absolutely necessary for drug efficacy. While we chose in RHAPSODY to allow patients treated with only IV rt-PA to allow broader generalization of the results, we suggest that other trialists may choose differently under different circumstances.

The selection criteria listed in Table Four represent a compromise between the need for ‘looser’ criteria to allow more rapid enrollment versus ‘tighter’ criteria to focus the study on patients most likely to respond. An upper limit on age is arbitrary, but needed for regulatory approval of the clinical trial protocol³². The limit on times (door to puncture, LKNW to revascularization) are the most important, because no variable impacts the likelihood of favorable outcome more than time^{33–35}. The lower limit on NIHSS serves to select a population more likely to show large vessel occlusion, a requirement for IAT³⁶. The requirement for demonstration of salvageable penumbra or limited volume of irretrievable core, or both, is controversial: while there is no sense—and some potential risk—in reperusing dead tissue, it is unclear whether current imaging methods unequivocally identify brain beyond salvage³⁷. Nevertheless, for acceptance at both regulatory and site-investigator levels, some limit on infarct volume seemed important.

Our findings should be interpreted with some limitations in mind. Most importantly, the 15 study sites in RHAPSODY are carefully selected and currently participate in the NINDS sponsored NeuroNEXT clinical trial network. The sites were selected through a competitive process, and have demonstrated commitment to clinical trial quality, regulatory compliance and recruitment/retention. They all joined the study simultaneously, and participation in competing clinical trials was discouraged. On the other hand, when NeuroNEXT was being organized there was no premium allotted to selecting study sites with demonstrated capability as comprehensive stroke centers. Thus, the trial includes some centers with world-class recognition for their neuro-interventional programs as well as other sites with more typical capabilities in delivering IAT. Therefore, our results would likely predict the experience to be seen in other clinical trials with a heterogeneous group of stroke centers. Another limitation is that the study material, 3K3A-APC, is relatively easy to administer: a simple 15 min infusion every 12 hours for 5 doses. More complex protective strategies, such as constant infusions that must be titrated, may be more difficult to implement. Another limitation is that IAT as a standard care treatment is only in its infancy. Likely the broad criteria we present here (Table Four) will be refined over time.

These findings raise a number of questions that must be addressed in future investigations. Site selection criteria will require refinement to optimize clinical trial execution without limiting the number of qualifying sites too severely: what is the impact of metrics such as door-to-needle time, door-to-puncture time, and recanalization success rates? The effect of transportation (drip-and-ship) on eligibility, consent, safety, and outcome is unknown. The timing of recanalization relative to study drug treatment may impact efficacy if, for example, the study drug can produce benefit only if administered before or only after recanalization. The effect of peri-interventional management may alter safety and outcome measures significantly: study is needed to assess the effect of local vs. general anesthesia; co-administration of anticoagulants, platelet inhibitors, and glycoprotein IIb/IIIa inhibitors; and use of proximal carotid stenting when required. Finally, the most significant opportunity offered by IAT—besides documented recanalization—is the capability to administer neuroprotection locally³⁸. While intriguing, the idea of administering an immediate, local dose of a putative neuroprotectant will require considerable development in terms of safety and possible efficacy.

Our data do not address whether recanalization is achieved with tPA alone, but some estimates suggest the rate could be as high as 50%³⁹. Post-rt-PA recanalization is rarely documented using imaging. The variability in definitions of measuring late recanalization begs for some standardization in how studies are measuring reperfusion, given the importance that has been placed on it. In future trials, some means of documenting recanalization in rt-PA-only patients will be needed.

In conclusion, it is feasible to include IAT in a neuroprotectant trial for acute ischemic stroke. Criteria are presented for including such patients in a manner that is consistent with evidence based support for IAT while still preserving the ability to test the role of the putative neuroprotectant.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Partners Human Research Affairs for coordination and implementation of the single IRB model.

Funding Sources. This study was funded by the National Institutes of Neurological Disorders and Stroke (U01NS088312). The NeuroNEXT Network is supported by the National Institutes of Neurological Disorders and Stroke (Clinical Coordinating Center: U01NS077179, Data Coordinating Center: U01NS077352).

PL is the recipient of U01 NS088312, and KP the recipient of X01 NS088312, both titled “A multi-center, Phase 2 study using a CRM to determine the safety and tolerability of 3K3A-APC in combination with tPA in moderately severe acute hemispheric ischemic stroke.” SW and KP are employees of, and HL is consultant to ZZ Biotech, LLC.

This report does not represent the official view of the National Institute of Neurological Disorders and Stroke (NINDS), the National Institutes of Health (NIH), or any part of the US Federal Government. No official support or endorsement of this article by the NINDS or NIH is intended or should be inferred.

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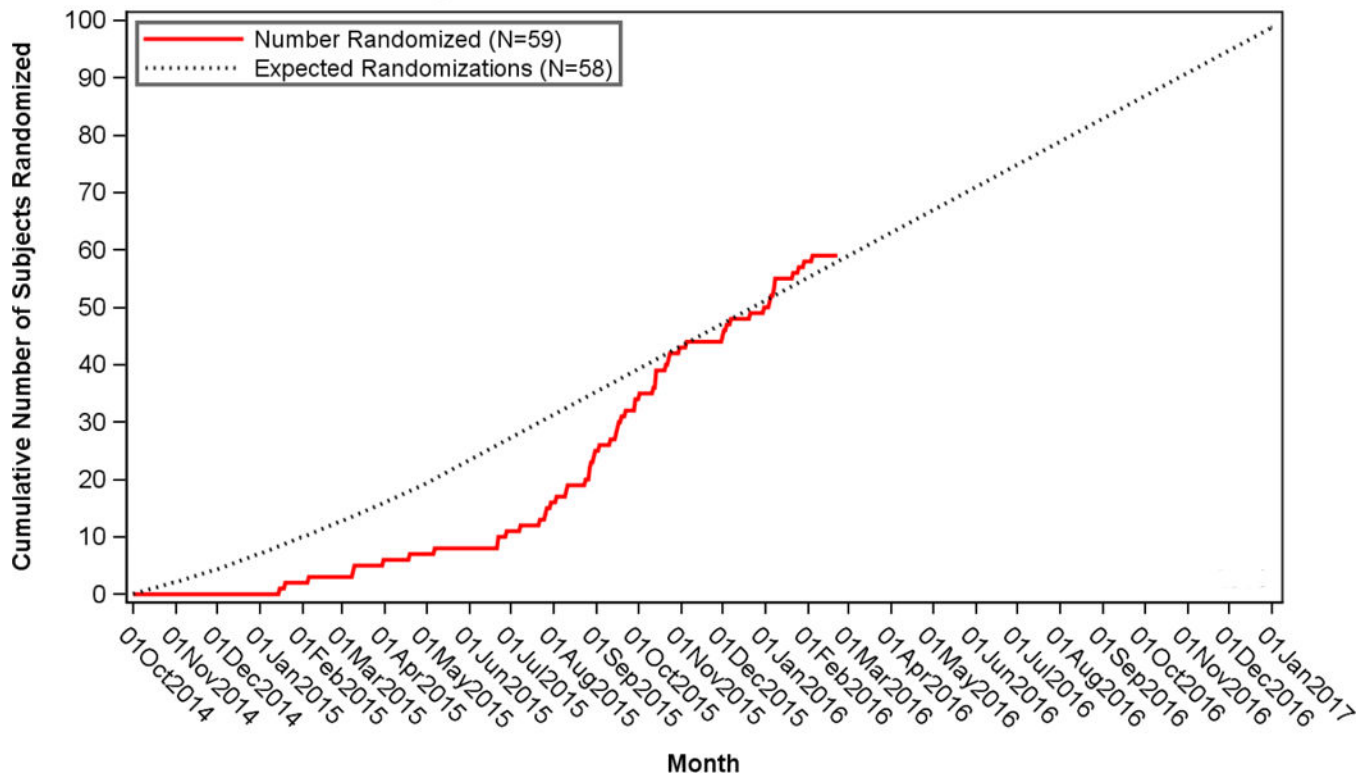


Figure. Recruitment, actual compared against expected

The cumulative recruitment into the RHAPSODY trial as of February 22nd, 2016 is shown from the beginning of the trial. The protocol amendment described here was approved in May 2015 (arrow), and took effect in June 2015. As sites finalized adoption of the new protocol, there was a dramatic increase in recruitment beginning in July 2015.

Table One
Selection Priorities in Standard Care vs. a Clinical Trial

Patient selection priorities in the standard care of patients seek to provide effective treatment safely to the widest possible range of patients. Such criteria should emphasize physician judgment in applying published data to single patients¹³. In contrast, clinical trial protocol selection criteria seek to focus the treatment on patients most likely to respond, thus demonstrating a beneficial treatment effect with the smallest number of patients¹⁴. In a clinical trial, adherence to the protocol assures optimal homogeneity of the final study sample.

Standard Care	Clinical Trial Protocol
Widest possible selection based on evidence	Narrower selection to prioritize consistency
Physician judgment, personalized care	Patient safety
	Optimize chances of patient benefit
	Avoid "off-label" procedures that could interfere with trial assessments
Professional Society Guidelines	Trial specific guidelines
Presumption of ELVO based on NIHSS, NCCT, CTA/MRA or DSA	Confirmed ELVO on baseline CTA/MRA
Wide range of upper age limits	Age limit based on neuroprotectant to be studied

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Table Two
Intra-arterial Trials' Study Factors Relevant to Neuroprotection

For the 5 major trials of IAT for acute stroke that showed benefit, the key factors are summarized. "Median time to IAT" is the median of the time from symptom onset (or last known well, LKW) to the initiation of the procedure, in minutes. "Max Time to IAT" is the maximum protocol-allowed time to initiate recanalization therapy after stroke symptom onset. Mean age, median NIHSS, and mean (or median in ESCAPE and MR CLEAN) time to bridging therapy with IV rt-PA were comparable in the groups compared in all studies.

Trial	Sample Size (n)	Median Time to IAT (min)	Max Time to IAT (hours)	Mean Age IA vs. Control (years)	Median NIHSS IA vs. Control	Median Time to IVT IA vs. Control (min)
ESCAPE	316	200	12	71/70	16/17	110/125
EXTEND-IA	70	210	6	69/70	17/13	127/145
MR CLEAN	500	260	6	66/66	17/18	85/87
REVASCAT	206	269	8	66/67	17/17	117/105
SWIFT PRIME	196	224	6	65/66	17/17	110/117

Table Three
Intra-arterial Trial Results Relevant to Neuroprotection

Recanalization is predicted to improve the odds of success in a neuroprotectant clinical stroke trial. The outcomes of most relevance in designing selection criteria for a neuroprotection trial are rates of successful reperfusion, eventual disability (mRS), symptomatic ICH, and mortality. Although trials reported successful recanalization at different times, we looked for “late” recanalization meaning sometime after the immediate treatment period, typically 24 hours following IAT.

Trial	Late Recanalization or Reperfusion (%) IA vs. Control	mRS 0–2 IA vs. Control	sICH (%) IA vs. Control	Mortality IA vs. Control
ESCAPE	72.4 [§] 31.2 [¶]	53\29.3	3.6\2.7	10.4\19.0
EXTEND-IA	89 [#] 34 [#] (86 [*] not reported)	71\40	0\6	9\20
MR CLEAN	84 [¶] 57.5 [¶] (58.7 [*] Not Reported)	32.6\19.1	7.7\6.4	21\22
REVASCAT	66 [*] Not Reported	43.7\28.2	1.9\1.9	18.4\15.5
SWIFT PRIME	83 ^{§§} 40 ^{§§}	60\35	0\3	9\12

* Defined as achieving the modified TICI 2b/3²⁹

§: Defined as achieving TICI score²⁹ of 2b/3.

¶: Defined as achieving mAOL score of 2 or 3³⁰.

#: Defined as reperfusion >90% without sICH.

§§: Defined as reperfusion = 90%.

Table Four
Selection Guidelines in a Neuroprotectant Trial

Based on our review of the published trials, as well as the user-survey from our 15 clinical trial sites, we were able to identify an allowed range of selection criteria. The “RHAPSODY Target” criteria are selected from the allowed range for our use in the RHAPSODY trial, but future clinical trialists could consider any value within the allowed range, based on their own considerations of the stroke population they wish to target. For example, an ASPECTS score above 7 was required by the RHAPSODY steering committee to elevate the presumed safety of this early-development, Phase 2 trial, even though some IAT trials admitted patients with more severe “core size” measurements.

Variable	Allowed Range	Target
Age (years)	< 80–90	<90
Time: door to Puncture (min)	90 to 120	90
Time: LKNW to revascularization (hours)	5 to 8	6
Devices	Any 2 nd or 3 rd generation device	Stent retrievers
NIHSS	5 to 32	>=5
Imaging Modality	CT or MRI	NCCT
Vascular imaging	ELVO on any modality	ELVO on CTA/MRA
Perfusion imaging	Mismatch	Salvageable penumbra
Core size	ASPECTS >6, CT hypo > 1/3, DWI > 70cc	ASPECTS > 7

Abbreviations: LKNW: last known normal or well. NCCT: non-contrast cranial computed tomography. ELVO: eligible large vessel occlusion. ASPECTS: Alberta Stroke Program Early CT Score. CT hypo: early hypodensity visible on NCCT. CTA: computed tomographic angiogram. DWI: diffusion weighted imaging hyperintensity.

Table Five
Exclusions due to age, NIHSS, time, and use of IAT before and after the protocol amendment

The criteria for both inclusion and exclusion changed with the protocol amendment, so the selection of patients for screening and for enrollment changed. There were dramatic decreases in the proportion of patients excluded for age, NIHSS, and time to presentation, which reflect the amended selection criteria. In addition, prior to the amendment 78 patients were excluded from the trial because they underwent IAT, a criterion that did not exist after the amendment. Enrollment increased dramatically from 1.3 to 6.2% of screened patients after the amendment. Due to the asymmetric sample sizes, and the fact that both screening and enrollment criteria changed, a statistical test of significance is not appropriate, but for illustration purposes only, the Fisher's Exact Test Odds Ratio [95%CL] for increased enrollment is 4.9 [2.3,10.4], with $p < 0.001$.

Selection Variable	Patients Excluded Before Protocol Amendment (% of Total Screened)	Patients Excluded After Protocol Amendment (% of Total Screened)
Age	130 (21.9)	29 (3.8)
NIHSS	270 (45.5)	162 (21.3)
Late (3 hours before; 6 hours after)	75 (12.6)	27 (3.6)
No. excluded for IAT	78 (13.1)	N/A
Total Enrolled and Treated	8 (1.3)	51 (6.2)
Total Screened	601	821